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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,541	02/27/2002	Tatsuya Haga	31671-176438	1435

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	11

DATE MAILED: 07/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,541	HAGA ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-98* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-10,14,19,20,26,34,37,64,65 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-7,11-13,15-18,21-25,27-33,35,36,38-63,66 and 68-98.

DETAILED ACTION

Election/Restrictions

1. Newly amended claim **1** now has the additional limitation of "expressed in a cholinergic neuron" which is an addition to the original limitation of "A gene", taken by the Examiner to be an isolated and/or substantially purified gene. Since Nikawa *et al.* (1990) taught the isolation and characterization of a choline transport gene, the reference anticipated claim 1 as originally presented.

2. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims **2-7, 11-13, 15-18, 21-25, 27-33, 35-36, 38-63, 66,** and **68-98** are withdrawn from consideration as being directed to non-elected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.The restriction/election requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

3. The Preliminary Amendments filed 27 February 2002 (Paper No. 8) and 24 February 2003 (Paper No. 10) have been received and entered in full. Claims 64-98 have been added. Claims 1, 24-27, 29-33, 35-38, 40-48, 50-52, and 56-63 have been amended.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims **1, 8, 9, 10, 14, 19,** and **20** are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The aforementioned claims are directed to "a gene", "DNA", and "a protein". All three are products of nature and therefore are non-statutory subject matter. This rejection may be obviated by amending the claims to read "An isolated gene", Substantially purified DNA", and "An isolated protein" or similar amendments to demonstrate the "hand of man" and thus to differentiate the claimed subject matter from naturally occurring products.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims **1, 8, 9, 10, 14, 20, 26, 34,** and **37** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated gene comprising an amino acid sequence represented by SEQ ID NO: 6 or a host cell transfected with same and a protein or fusion protein comprising SEQ ID NO: 6,* does not reasonably provide enablement for *a protein comprising an amino acid sequence where one or a few amino acids are deficient, substituted, or added in the amino acid sequence represented by SEQ ID NO: 6 or a protein comprising an amino acid sequence where one or a few amino acids are deficient, substituted, or*

added in the amino acid sequence represented by SEQ ID NO: 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

6. Regarding derivatives and fragments of SEQ ID NO: 6, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495].

7. For instance, Okuda *et al.* (22 November 2002) "Single nucleotide polymorphism of the human high affinity choline transporter alters transport rate." The Journal of Biological Chemistry **277**(47): 45315-45322 teaches that the presence of a single nucleotide polymorphism in the human CHT1 polymorphism in the human CHT1 gene (I89V) results in a 40-50% decrease in V(max) for choline uptake rate compared with the wild type. However, there was no

alteration in the apparent affinities for choline, sodium, chloride, and the specific inhibitor hemicholinum-3. (Figures 3, 4, and 6). Thus a single amino acid change can significantly reduce the activity of a high-affinity choline transporter.

8. In this regard, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome

annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims **1, 8, 9, 10, 14, 20, 26, 34,** and **37** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. The claims are drawn to gene encoding polypeptides and polypeptides having high-affinity choline transporter activity. The claims do not require that the polypeptide possess any particular conserved structure. Thus, the claims are drawn to a genus of polypeptides that is defined by a broad activity.

11. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a relatively defined function. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 6. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

12. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

13. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

14. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 6, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

15. Claims **64**, **65** and **67** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an in vitro preparing method of a cell having high-affinity choline transport activity characterized in introducing DNA encoding SEQ ID NO: 5 into said cell and the cell made by said in vitro method*, does not reasonably provide enablement for *the practicing of said method in vivo (i.e. in patients) or transgenic animals made by the claimed method*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

16. The above invention is drawn to methods of transfecting a cell with a DNA encoding a protein with high-affinity choline transporter activity. The language of said claims encompasses both *in vivo* and *in vitro* transfection (DNA introduction). The specification teaches that DNA encoding a protein with high-affinity choline transporter activity can be successfully introduced into oocytes and COS7 cells.

17. But the claims are drawn very broadly to methods of introducing DNA encoding a protein with high-affinity choline transporter activity into cell lines and patients (i.e. gene

therapy). Since the specification fails to provide any guidance for the successful introduction of a DNA encoding a protein with high-affinity choline transporter activity into a patient (whether human or animal) and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

18. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of introducing a DNA encoding a protein with high-affinity choline transporter activity into an animal. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific DNA encoding a protein with high-affinity choline transporter activity *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* gene therapy or to make transgenic animals, such a disclosure would not be considered enabling since the state of gene therapy is highly unpredictable [see Verma and Somia (18 September 1997) "Gene therapy- promises, problems, and prospects." Nature **389**: 239-241; Kaneda (September 2001) "Gene Therapy: A Battle Against Biological Barriers" Current Molecular Medicine **1**(4): 493-499; Eck and Wilson (1996) Chapter 5: "Gene-Based Therapy" **Goodman & Gilmans's The Pharmacological Basis of Therapeutics 9th Ed.** (pp. 77-100)] The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

19. The following references are cited herein to illustrate the state of the art of a gene encoding a protein with high-affinity choline transporter activity.

20. Regarding derivatives and fragments of DNA encoding SEQ ID NO: 6, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495].

21. For instance, Okuda *et al.* (22 November 2002) "Single nucleotide polymorphism of the human high affinity choline transporter alters transport rate." The Journal of Biological Chemistry **277**(47): 45315-45322 teaches that the presence of a single nucleotide polymorphism in the human CHT1 polymorphism in the human CHT1 gene (I89V) results in a 40-50%

decrease in V(max) for choline uptake rate compared with the wild type. However, there was no alteration in the apparent affinities for choline, sodium, chloride, and the specific inhibitor hemicholinum-3. (Figures 3, 4, and 6). Thus a single amino acid change can significantly reduce the activity of a high-affinity choline transporter.

22. In this regard, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in

the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

23. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of conditions for successful incorporation of a DNA encoding a protein with high-affinity choline transporter activity into the genome of an animal. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* transfection of a gene encoding a protein having high-affinity choline transporter activity as exemplified in the references above.

24. Claim **9** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

25. Claim 9 recites: "SEQ ID NO: 5 or its complementary sequence and a part or whole of these sequences". It is unclear whether claim 9 is directed to a fusion or was intended to recite all in the alternative.

26. Claim **10** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. The term "stringency" in claim 10 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

28. Claims **20, 26,** and **37** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

29. Claims 20, 26, and 37 refer to "human high-affinity choline transporter activity". It is not clear from the instant Specification or the prior art as to what the metes and bounds of "human high-affinity choline transporter activity" are.

30. Claims **26** and **37** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

31. Claims 26 and 37 refer to high-affinity choline transporter activity or claim 20 but claim 20 does not provide further details of such activity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

32. Claims **1** and **9** are rejected under 35 U.S.C. 102(b) as being anticipated by Slotkin *et al.* (August 1994) "Overexpression of the High Affinity Choline Transporter in Cortical Regions Affected by Alzheimer's Disease." J. Clin. Invest. **94**(2): 696-702. Slotkin *et al.* teaches the isolation of brain tissue from control and Alzheimer's patients following death and the assaying of said tissue for activity of a high affinity choline transporter in neurons (Figure 1). Slotkin *et al.* teaches that the cholingeric neurons in Alzheimer's patients show an increased expression of a high affinity choline transporter thus meeting the limitations of claim 1 (pp. 700-701). Further, the cholingeric neurons in Alzheimer's patients showing an increased expression of a high affinity choline transporter by default express a part (at least one bp) and may well express the whole of SEQ ID NO: 5 thus meeting the limitations of claim 9 (pp. 701).

33. Claims **9, 14, 20, 34,** and **37** are rejected under 35 U.S.C. 102(b) as being anticipated by Nikawa *et al.* (15 September 1990) "Primary Structure of the Yeast Choline Transport Gene and

Regulations of its Expression." The Journal of Biological Chemistry **265**(26): 15996-16003 (**IDS #A16**). Nikawa *et al.* teaches a choline transporter gene and the accompanying amino acid sequence thus meeting the limitations of claims 9, 14, and 20 (Figures 4 and 7; Table 1). Nikawa *et al.* teaches yeast cells expressing a choline transporter and showing choline transporter activity thus meeting the limitations of claims 34 and 37 (Figure 9 and 10).

34. Claim **14** is rejected under 35 U.S.C. 102(b) as being anticipated by Knipper *et al.* (18 June 1991) "Purification and reconstitution of the high affinity choline transporter." Biochimica et Biophysica Acta. **1065**(2): 107-113. Knipper *et al.* teaches the purification and functional characterization of a protein with high affinity choline transporter activity thus meeting the limitations of claim 14 (Figures 5 and 6; pp. 113).

Summary

35. Claims 1, 8-10, 14, 19-20, 26, 34, 37, 64, 65, and 67 are hereby rejected.

36. The following articles, patents, and patent applications were found by the Examiner during the art search and are here made of note:

a. US 6500643 B1 (31 December 2002) Wu *et al.*

b. US 2003/0022195 A1 (30 January 2003) Curtis

c. US 2003/0114399 A1 (19 June 2003) Blakely *et al.*

d. Apparsundaram *et al.* (5 October 2000) "Molecular Cloning of a Human, Hemicholinium-3-Sensitive Choline Transporter." Biochemical and Biophysical Research Communications **276**(3): 862-867.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
June 27, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER